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Original Research

Determination of potential drug-drug interactions with different interaction software programs in elderly patients over 85 in a community pharmacy setting: A cross-sectional study

Harun Kızılay[1], Cengizhan Ceylan[2]
[1] Department of Pharmacology
[2] Department of Clinical Pharmacy, Faculty of Pharmacy, Selcuk University, Konya, Turkey

Abstract

Aim: Various potential drug-drug interaction screening software programs or databases have been developed and implemented as decision support tools to assist clinicians. The risk of adverse drug reactions, hospitalization, compliance problems, and potential drug-drug interactions increases with age. Our research aimed to detect potential drug-drug interactions in elderly patients over 85 and compare the software programs used to detect interactions.

Material and Methods: Prescriptions of elderly patients over the age of 85 who received their medications from five different community pharmacies in Konya, Türkiye, in 2022 were retrospectively examined. The software programs Medscape®, Drugs®, Micromedex®, and LexiComp® were used to detect potential drug-drug interactions and reveal common interactions in the patients. The compatibility of the programs was also determined.

Results: A total of 307 patients (43.3% male and 56.7% female) were included in this study. While Micromedex® detected a total of 920 interactions in the total sample, Medscape® detected 1,876, Drugs® detected 1,632, and LexiComp® detected 1,414. However, LexiComp® detected the most contraindications. Regarding the compatibility of the four software programs, Kendall's W value was calculated as 0.79, and the statistical significance was determined ($p < 0.05$).

Discussion: Medscape®, Drugs®, Micromedex®, and LexiComp® software programs used to detect potential drug-drug interactions in the elderly exhibit high compatibility with each other. It is recommended that clinicians use more than one software program to determine potential drug-drug interactions for rational drug use.

Keywords

Geriatrics, Aged, Drug Interactions, Pharmacy, Aging

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Corresponding Author: Harun Kızılay, Department of Pharmacology, Faculty of Pharmacy, Selcuk University, Konya, Turkey.
E-mail: harunkizilay@gmail.com P: +90 532 307 77 41
Corresponding Author ORCID ID: https://orcid.org/0000-0003-3660-0721
Other Author ORCID ID: Cengizhan Ceylan, https://orcid.org/0000-0003-4164-9212
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Introduction

Drug-drug interactions (DDIs) are defined as situations in which the pharmacological effect of one drug is altered by another when two drugs are used together. The most important reason why drug interactions are common is the use of multiple drugs at the same time [1]. DDIs are a particularly important type of adverse drug event because they can alter drug effectiveness and safety. While DDIs may not always be preventable, they can often be predicted [2, 3]. Actual DDIs are determined from adverse outcomes in patients, whereas potential DDIs (pDDIs) are those identified through analysis of the pharmacokinetic and pharmacodynamic profiles of each drug in use and the identification of potential adverse events resulting from this association. pDDIs may present with adverse outcomes in patients or have no clinical consequence [3-6]. The prevalence of pDDIs in the community pharmacy setting may vary depending on age and disease [7].

Various pDDI screening software programs or databases have been developed and implemented as decision support tools to assist clinicians [8]. These tools frequently report whether pDDIs identified occur due to the pharmacokinetic and/or pharmacodynamic effect, highlight the degree of severity, outline the management of pDDIs and provide reference literature. However, some databases do not include all of these components [9].

Polypharmacy is the use of multiple medications. Although there is no clear definition for polypharmacy, the simultaneous use of five or more drugs is generally accepted [10]. As drug use increases, drug-drug interactions will also increase and adverse drug reactions (ADRs) may be observed accordingly [11].

Old age is defined as age 65 and above. The increase in chronic comorbidities and pharmacokinetic and pharmacodynamic changes with age make elderly patients more sensitive to drug side effects [12]. The risk of ADRs, hospitalization, compliance problems, and pDDIs increases with age [9, 13]. The MULTIPAP Study, conducted on elderly patients treated in Spanish primary care centers, indicated that half of the patients had DDIs at least once. Similarly, a cross-sectional study conducted in Brazil reported that the prevalence of DDIs among elderly patients using multiple medications was around 35%. DDIs constitute a part of ADRs. In fact, it is estimated that 6%–30% of all ADRs in the population are caused by DDIs and are therefore largely preventable. Hence, continuous monitoring of inappropriate prescriptions that may lead to DDIs at the patient and/or population level is an important activity for ADRs prevention [14-17]. Our research aimed to detect pDDIs in elderly patients and compare software programs used to detect interactions.

Material and Methods

Prescriptions of elderly patients over 85 who received their medications from five different community pharmacies in Konya, Türkiye, from January 1 to December 31 2022 were retrospectively examined. Patients' age, gender, and medication information were recorded, and prescriptions containing medications not covered by the software programs were excluded. The software programs Medscape®, Drugs®, Micromedex®, and LexiComp® were used to detect pDDIs in the patients.

While Medscape® and Drugs® accept free memberships, LexiComp® and Micromedex® accept paid memberships. Interaction classifications of software programs are shown in Figure 1.

Statistical Analyses

By analyzing each pDDI using Kendall's W values, the link between the prospective pDDI software programs was verified based on the outcomes of severity degrees of interaction. Kendall's W values range from 0–0.2, which denotes a little agreement, to 0.21–0.40 (fair), 0.41–0.60 (considerable), 0.61–0.80 (significant), and 0.81–1.0 (perfect). IBM SPSS 22.0 was used to conduct the statistical analysis. The threshold of statistical significance was set at $p < 0.05$.

Ethical Approval

This study was approved by the Ethics Committee of Selçuk University Faculty of Medicine Local Ethics Committee (Date: 2022-06-22, No: E.304008).

Results

A total of 307 patients (43.3% male and 56.7% female) were included in this study. While the average age of male patients was 88.38, it was 88.51 for females. While male patients had an average of 6.44 medications in their prescriptions, this number for females was 6.62. Polypharmacy was detected in the prescriptions of 223 (72.63%). Details are given in Table 1. While Micromedex® detected a total of 920 interactions in the total study sample, Medscape® detected 1,876, Drugs® detected 1,632, and LexiComp® detected 1,414 interactions. While Micromedex® detected 1 contraindicated interaction, Medscape® detected 4 and LexiComp® detected 79 contraindicated interactions. The number of interactions per patient in Micromedex®, Medscape®, Drugs®, and LexiComp® were 2.99, 6.11, 5.31, and 4.6, respectively. Details are given in

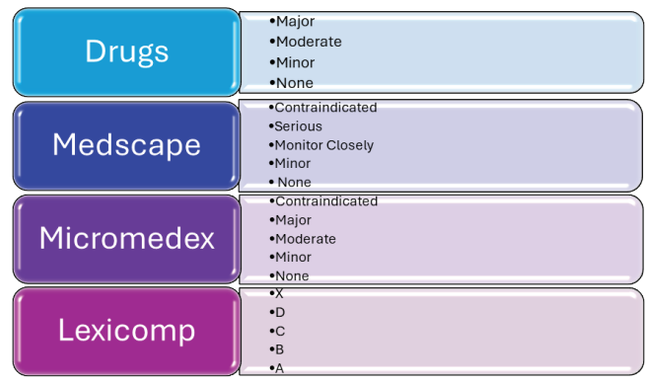

Figure 1. Classification of potential drug-drug interactions

Table 1. Patient demographics status

	Gender	
	Male	Female
Number of patients (N, %)	133 (43.3%)	174 (56.7%)
Age (mean, SD)	88.38±2.88	88.51±3.25
Number of drugs (mean, SD)	6.44±3.03	6.62±2.77
Polypharmacy (N,%) + -	90 (29.31%) 43 (14%)	133 (43.32%) 41 (13.35%)

SD: Standard deviation

Table 2. Total number of potential drug-drug interactions detected by different software programs

	Micromedex			Medscape			Drugs			LexiComp		
	Contraindicated	Major	Total	Contraindicated	Serious	Total	Major	Moderate	Total	X	D	Total
Total (n) (%)	1 0.1%	572 62.17%	920	4 0.21%	142 7.56%	1876	152 9.31%	1234 75.61%	1632	79 5.58%	183 12.94%	1414
NDDIP (n)	0.01	1.86	2.99	0.003	0.46	6.11	0.49	4.01	5.31	0.59	0.25	4.6

NDDIPP: Number of drug–drug interactions per patient

Table 3. Evaluation of different software programs and examples of contraindicated interactions

Programs	Kendall's W	Chi-square	p-value
Micromedex®-Medscape®-Drugs®-LexiComp®	0.79	977.78	p < 0.05
Micromedex®-Medscape®	0.86	529.73	p < 0.05
Micromedex®-Drugs®	0.83	510.63	p < 0.05
Micromedex®-LexiComp®	0.86	525.9	p < 0.05
Medscape®-Drugs®	0.90	549.49	p < 0.05
Medscape®-LexiComp®	0.85	521.99	p < 0.05
Drugs®-LexiComp®	0.89	541.65	p < 0.05

pDDIs Software Program	pDDIs (n)	Comment
Micromedex®	Metoclopramide-Sertraline (1)	Increases the risk of extrapyramidal reactions and neuroleptic malignant syndrome.
Medscape®	Clarithromycin-Indapamide (1)	Increases QTc interval.
	Moxifloxacin-Indapamide (1)	Increases QTc interval.
	Amisulpride-Olanzapine (1)	Increases the risk of neuroleptic malignant syndrome.
	Amisulpride-Quetiapine (1)	Increases the risk of neuroleptic malignant syndrome.
LexiComp®	Esomeprazol-Clopidogrel (3)	Esomeprazole may diminish the antiplatelet effect of Clopidogrel.
	Diclofenac-Ketoprofen (4)	Nonsteroidal anti-ınflammatory agents may enhance the adverse/toxic effects of other nonsteroidal anti-ınflammatory agents, particularly the risk of gastrointestinal toxicity.
	Etodolac-Ibuprofen (1)	
	Dexketoprofen-Indomethacin (1)	
	Ketoprofen-Metamizole (2)	
	Flurbiprofen-Ketoprofen (2)	
	Ibuprofen-Ketoprofen (3)	
	Celecoxib-Etodolac (1)	
	Celecoxib-Naproxen (1)	
	Etodolac-Naproxen (1)	
	Diclofenac-Flurbiprofen (2)	
	Diclofenac-Mefenamic acid (1)	
	Flurbiprofen-Mefenamic acid (1)	
	Ibuprofen-Nimesulide (1)	
	Celecoxib-Diclofenac (1)	
	İbuprofen-Indometacin (1)	
	Indometacin-Ketoprofen (1)	
	Ketoprofen-Naproxen (1)	
	Diclofenac-İbuprofen (1)	
	Ipratropium and Albuterol- Fluticasone, Umeclinidum and Vilanterol (5)	Umeclidinium may enhance the anticholinergic effect of anticholinergic agents. Ipratropium (oral inhalation) may enhance the anticholinergic effect of other anticholinergic agents
	Ipratropium- Ipratropium and Albuterol (3)	Beta2-agonists (Short-Acting) may enhance the adverse/toxic effects of other Beta2-Agonists
	Enoxaparin-Apixaban (2)	Apixaban may enhance the anticoagulant effect of Anticoagulants.
	Ipratropium- Ipratropium and Albuterol (3)	Beta2-Agonists (Short-Acting) may enhance the adverse/toxic effect of other Beta2-Agonists
	Tiotropium-Ipratropium and Albuterol (8)	Anticholinergic agents may enhance the anticholinergic effect of tiotropium
	Other (29)	

pDDIs: potential Drug-Drug Interactions

Table 2. When the compatibility of the four software programs was examined, Kendall's W was calculated as 0.79, and statistical significance was determined ($p < 0.05$). The compatibility of the software programs among themselves was also investigated. In the compatibility analysis between Micromedex®, Medscape®, and LexiComp®, Kendall's W was determined as 0.81 ($p < 0.05$). When pairwise comparisons were made between programs, the highest score was between Medscape® and Drugs® (Kendall's W: 0.9, $p < 0.05$). When Kendall's W values were examined, it was determined that the software programs were highly compatible with each other. LexiComp® detected that 32.9% of contraindicated interactions were caused by combinations of nonsteroidal anti-inflammatory drugs (NSAIDs). Common contraindicated interactions, as well as their potential effect, details are given Table 3. Metoclopramide/Sertraline was identified as a contraindicated combination in Micromedex® software program. In Medscape®, Clarithromycin/Indapamide, Moxifloxacin/Indapamide, Amisulpride/Olanzapine and Amisulpride/Quetiapine combinations were identified as contraindicated. In the LexiComp® software program, combinations such as Diclofenac/Ketoprofen, Diclofenac/Ketoprofen, Diclofenac/Ketoprofen, Diclofenac/Ketoprofen and Flurbiprofen/Ketoprofen were found to be contraindicated.

Discussion

With age, there is increased physiological changes that may alter the effect of a drug, making the elderly population more prone to ADRs. Therefore, pDDI management is crucial. Clinicians benefit from various software programs for pDDI management. These programs can predict clinically important pDDIs and ADRs. Comparing the differences between such software programs should guide clinicians in predicting critical events [18, 19].

In this research, four frequently used interaction software programs were compared. While Medscape® and Drugs® are free to use, LexiComp® and Micromedex® require paid membership. It is thought that the free-to-use option increases the use of Medscape® and Drugs® in the community pharmacy environment. Most pDDIs were detected in Medscape®. The program with the least interaction was Micromedex®. Medscape® explains an interaction with more than one mechanism, and this is thought to be the reason for the difference. The most contraindications were detected in LexiComp®. It is thought that this is because this software program is provides an extensive list of contraindications, especially regarding NSAID combinations. There is no contraindication warning for the combined use of NSAIDs in other software programs

In a study involving patients aged 65 and over, Liu et al. indicated moderate agreement (weighted kappa = 0.473) between LexiComp® and Micromedex®. Furthermore, LexiComp® detected the most contraindicated interactions [20]. Howeever, the present study found a high difference between LexiComp® and Micromedex® (Kendall's W = 0.86). In a study conducted in a community pharmacy environment, Sancar et al. determined that Micromedex®, Medscape®, and Drugs® were highly compatible with each other [21]. The present study found a similar result between the three programs (Kendall's W > 0.80). In Kheshti et al.'s study, which compared five commonly used drug interaction databases (LexiComp®, Micromedex®, iFacts®, Medscape®, and Epocrates®), LexiComp® and Micromedex® were found to be more suitable than other databases for determining clinically important drug interactions [22]. In a study comparing Micromedex®, LexiComp®, and Drugs® for intensive care patients receiving antibiotics, 15% of the interactions detected with Micromedex®, 28.6% of the interactions detected with Medscape®, and 19.8% of the interactions detected with Drugs® were found to be significant [23].

Combinations of NSAIDs are remarkable, especially when contraindicated interactions are examined in LexiComp®. It has been stated that the risk of bleeding increases because of this interaction. Clinicians should be careful when prescribing these combinations in elderly patients. Complications that may develop due to bleeding can turn into life-threatening problems in such patients. Additionally, caution should be exercised when prescribing anticoagulant drugs in the elderly due to the risk of bleeding [24]. Drug interactions should always be considered in patients receiving anticoagulant therapy, especially those with multiple comorbidities, to optimize treatment [25].

Limitation

Conducting this study retrospectively was the most important limiting factor. Hence, limited data were obtained, and the number of drug interactions detected that were clinically significant could not be determined. Multicenter and larger prospective studies are needed to eliminate these limitations.

Conclusion

Interaction programs used to detect pDDIs in elderly patients in the community pharmacy setting demonstrate high compatibility. However, there are some differences in interaction severity among these programs; therefore, it would be appropriate to use a combination of programs when detecting pDDIs.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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